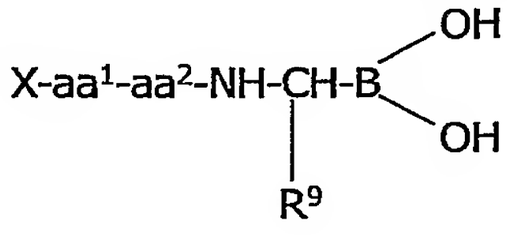
CLAIMS

1. A compound selected from boronic acids of formula (I), and pharmaceutically acceptable salts, prodrugs and pharmaceutically acceptable prodrug salts thereof:



(I)

wherein

X is H (to form $NH_2$) or an amino-protecting group;

$aa^1$ is an amino acid residue having a side chain selected from formula (A) and (B):

$$-(CO)_a-(CH_2)_b-D_c-(CH_2)_d-E \qquad (A)$$

$$-(CO)_a-(CH_2)_b-D_c-C_e(E^1)(E^2)(E^3) \qquad (B)$$

wherein

a is 0 or 1;

e is 1;

b and d are independently 0 or an integer such that (b+d) is from 0 to 5 or, as the case may be, (b+e) is from 1 to 5;

c is 0 or 1;

D is O or S;

E is a saturated or unsaturated cyclic hydrocarbyl group which normally contains up to 14 members; and

$E^1$, $E^2$ and $E^3$ are each independently selected from the group consisting of 5-6 membered saturated or unsaturated hydrocarbyl rings, or one of $E^1$, $E^2$ and $E^3$ is hydrogen and the other two are a said hydrocarbyl ring,

and wherein E, $E^1$, $E^2$ and $E^3$ are halogenated;

$aa^2$ is a residue of an amino acid which binds to the thrombin S2 subsite; and

$R^9$ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or $R^9$ is $-(CH_2)_m$-W where m is from 2, 3, 4 or 5 and W is –OH or halogen.

2. A compound of claim 1 wherein $R^9$ is an alkoxyalkyl group.

3. A compound of claim 1 or claim 2 wherein E, $E^1$, $E^2$ and $E^3$ are each independently selected from the group consisting of halogenated 6-membered rings.

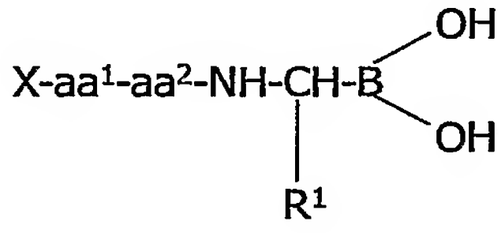
4. A compound of any of claims 1 to 3 wherein a and c are both 0 and (a+b+c+d) and (a+b+c+e) are 1, 2 or 3, particularly 1.

5. A compound of claim 4 wherein $aa^1$ is of (R)-configuration, $aa^2$ is of (S)-configuration, and the fragment $-NHCH(R^9)-B(OH)$ is of (R)-configuration.

6. A compound of any of claims 1 to 6 wherein said at least one substituent comprises halogen, hydroxy, amino, nitro, carboxyl or esterified carboxyl.

7. A compound of any of claims 1 to 6 wherein E, $E^1$, $E^2$ and $E^3$ are fluorinated.

8. A compound selected from boronic acids of formula (II), and salts, prodrugs and prodrug salts thereof:




(II)

where:

X is H (to form $NH_2$) or an amino-protecting group;

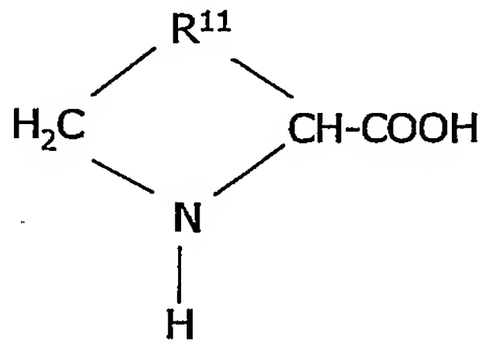
$aa^1$ is an amino acid having a side chain which is $C_1$-$C_5$ alkyl substituted by one or two moieties selected from fluorophenyl, cyclohexyl and fluorocyclohexyl;

$aa^2$ is an imino acid having from 4 to 6 ring members;

$R^1$ is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is –OH, –OMe, –OEt or halogen (F, Cl, Br or I).

9. A compound of claim 8 to claim 9 wherein $aa^1$ is selected from 4-F-Phe, 4-F-Dpa, 4-F-Dcha and 4-F-Cha.

10. A compound of claim 8 wherein $aa^2$ is a residue of an imino acid of formula (IV)



(IV)

where $R^{11}$ is $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, which group, when the ring is 5- or 6- membered, is optionally substituted at one or more $-CH_2-$ groups by from 1 to 3 $C_1$-$C_3$ alkyl groups, and optionally $aa^2$ is an (S)-proline residue, e.g. $aa^1$-$aa^2$ is (R)-Phe-(S)-Pro.

11. A compound of any of claims 8 to 10 wherein $aa^1$ is of (R)-configuration and/or $aa^2$ is of (S)-configuration and/or the fragment $-NH-CH(R^1)-B(OH)_2$ is of (R)-configuration.

12. A compound of any of claims8 to 12 wherein $R^1$ is 2-bromoethyl, 2-chloroethyl, 2-methoxyethyl, 3-bromopropyl, 3-chloropropyl or 3-methoxypropyl, e.g. is 3-methoxypropyl.

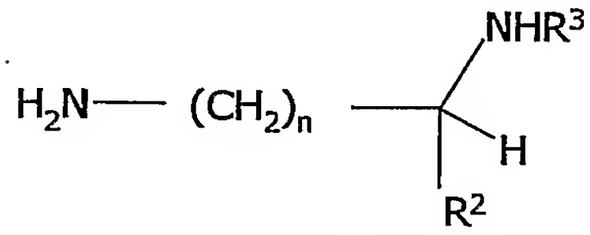
13. A compound of any of claims 8 to 13 where X is $R^6-(CH_2)_p-C(O)-$, $R^6-(CH_2)_p-S(O)_2-$, $R^6-(CH_2)_p-NH-C(O)-$ or $R^6-(CH_2)_p-O-C(O)-$ wherein p is 0, 1, 2, 3, 4, 5 or 6 and $R^6$ is H or a 5 to 13-membered cyclic group optionally substituted by one or more (e.g. 1, 2, 3, 4 or 5) halogens (e.g. F), for example at least at the 4-position, and/or by 1, 2 or 3 substituents selected from amino, nitro, hydroxy, a $C_5$-$C_6$ cyclic group, $C_1$-$C_4$ alkyl and $C_1$-$C_4$ alkyl containing, and/or linked to the cyclic group through, an in-chain O, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a $C_5$-$C_6$ cyclic group, and optionally said 5 to 13-membered cyclic group is aromatic or heteroaromatic, e.g. is phenyl or a 6-membered heteroaromatic group, for example X is benzyloxycarbonyl.

14. A compound of claim 8 or claim 13 wherein the boronic acid is of formula (VIII):

X-(R)-4-F-Phe-(S)-Pro-Mpg-$B(OH)_2$ (VIII).

15. A compound of any preceding claim which is in the form of a base addition salt of the boronic acid.

16. A compound of claim 15 which comprises a salt of the peptide boronic acid with an alkali metal or a strongly basic organic nitrogen-containing compound, and optionally wherein the strongly basic organic nitrogen-containing compound is a guanidine, a guanidine analogue or an amine, e.g. comprises a salt of the boronic acid with an alkali metal, an aminosugar, a guanidine, an amine of formula (XI):



(XI)

where n is from 1 to 6, $R^2$ is H, carboxylate or derivatised carboxylate, $R^3$ is H, $C_1$-$C_4$ alkyl or a residue of a natural or unnatural amino acid, e.g. a salt with lysine, arginine or a glucamine.

17. A compound of claim 15 which comprises a salt of the boronic acid with a metal.

18. A compound of claim 17 wherein the metal comprises an alkali metal salt, e.g. sodium or lithium.

19. A compound of any of claims 15 to 18 which comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

20. A pharmaceutical formulation comprising a compound of any of claims 1 to 19.

21. A pharmaceutical formulation of claim 20 which is adapted for intravenous administration or for subcutaneous administration, e.g. comprises the compound in the form of a finely divided solid for reconstitution as a solution ready for administration.

22. A pharmaceutical formulation of claim 20 which is adapted for oral administration, e.g. is a tablet capsule or is a particulate formulation in a sachet.

23. The use of a compound of claims 1 to 19 for the manufacture of a parenteral medicament for treating thrombosis, e.g. an acute coronary syndrome (for example acute myocardial infarction), a venous thromboembolic event (for example deep vein thrombosis or pulmonary embolism), for preventing thrombosis in a haemodialysis circuit of a patient, for preventing a cardiovascular event in a patient with end stage renal disease, for preventing venous thromboembolic events in a patient receiving chemotherapy through an indwelling catheter, for preventing thrombosis during a coronary artery by bypass graft operation, or for preventing thromboembolic events in a patient undergoing a lower limb arterial reconstructive procedure.

24. A parenteral pharmaceutical formulation comprising a combination of (i) a compound as defined in any of claims 1 to 19 and (ii) a further pharmaceutically active agent, for example another cardiovascular treatment agent, e.g. a lipid-lowering drug, a fibrate, niacin, a statin, a CETP inhibitor, a bile acid sequestrant, an anti-oxidant, a IIb/IIIa antagonist, an aldosterone inhibitor, an A2 antagonist, an A3 agonist, a beta-blocker, acetylsalicylic acid, a loop diuretic, an ace inhibitor, an antithrombotic agent with a different mechanism of action, an antiplatelet agent, a thromboxane receptor and/or synthetase inhibitor, a fibrinogen receptor antagonist, a prostacyclin mimetic, a phosphodiesterase inhibitor, an ADP-receptor ($P_2$ T) antagonist, a thrombolytic, a cardioprotectant or a COX-2 inhibitor.

25. A medicament comprising a salt, sugar ester or other soluble derivative of a boronic acid which is a selective thrombin inhibitor and has a neutral aminoboronic acid residue capable of binding to the thrombin S1 subsite linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, the hydrophobic moiety comprising a fluorinated ring in its S3-binding part and the salt comprising a cation having a valency n and having an observed stoichiometry consistent with a notional stoichiometry (boronic acid:cation) of n:1.

26. A method for making a product, comprising: contacting a boronic acid as defined in any of claims 1 to 14 with a pharmaceutically acceptable base to form the product.

27. The method of claim 26 which further comprises formulating the product into a pharmaceutical formulation.